



REVIEW

Recent advances in understanding rhinovirus immunity [version 1; peer review: 4 approved]

Spyridon Makris , Sebastian Johnston

National Heart and Lung Institute, Medical Research Council and Asthma UK Centre in Allergic Mechanisms of Asthma, Imperial College London, London, UK

v1 **First published:** 24 Sep 2018, 7(F1000 Faculty Rev):1537 (<https://doi.org/10.12688/f1000research.15337.1>)**Latest published:** 24 Sep 2018, 7(F1000 Faculty Rev):1537 (<https://doi.org/10.12688/f1000research.15337.1>)**Abstract**

Rhinoviruses are the most common cause of upper respiratory tract infections. However, they can induce exacerbations of chronic obstructive pulmonary disease and asthma, bronchiolitis in infants, and significant lower respiratory tract infections in children, the immunosuppressed, and the elderly. The large number of rhinovirus strains (currently about 160) and their antigenic diversity are significant obstacles in vaccine development. The phenotype of immune responses induced during rhinovirus infection can affect disease severity. Recognition of rhinovirus and a balance of innate responses are important factors in rhinovirus-induced morbidity. Immune responses to rhinovirus infections in healthy individuals are typically of the T helper type 1 (Th1) phenotype. However, rhinovirus-driven asthma exacerbations are additionally characterised by an amplified Th2 immune response and airway neutrophilia. This commentary focuses on recent advances in understanding immunity toward rhinovirus infection and how innate and adaptive immune responses drive rhinovirus-induced asthma exacerbations.

Keywords

Rhinoviruses, Asthma,

Open Peer Review**Reviewer Status** 

	Invited Reviewers			
	1	2	3	4
version 1				
published 24 Sep 2018				

F1000 Faculty Reviews are commissioned from members of the prestigious **F1000 Faculty**. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the reviewers are listed below, but their reports are not formally published.

- 1 **Zhao-Jun Duan**, Chinese Center for Disease Control and Prevention, Beijing, China
- 2 **Reena Ghidyal**, University of Canberra, Canberra, Australia
- 3 **Ville Peltola**, University of Turku and Turku University Hospital, Turku, Finland
- 4 **Larry J Anderson**, Emory University, Atlanta, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Spyridon Makris (s.makris@imperial.ac.uk)

Author roles: **Makris S:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Johnston S:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2018 Makris S and Johnston S. This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Makris S and Johnston S. **Recent advances in understanding rhinovirus immunity [version 1; peer review: 4 approved]** F1000Research 2018, 7(F1000 Faculty Rev):1537 (<https://doi.org/10.12688/f1000research.15337.1>)

First published: 24 Sep 2018, 7(F1000 Faculty Rev):1537 (<https://doi.org/10.12688/f1000research.15337.1>)

Introduction

Rhinoviruses (RVs) are the main cause of common colds and are responsible for the majority of acute exacerbations of chronic obstructive pulmonary disease (COPD) and asthma^{1,2}. Despite being discovered over 50 years ago, RVs have no effective anti-viral treatment or vaccine. Recently, the number of RV strains identified increased to about 160 RV strains/subtypes. RVs are divided into three species—RV-A, -B, and -C—on the basis of genetic classification. Species A and B are also classified on the basis of the cell surface receptor used for cellular entry. The “major group” of RVs, which includes about 90% of the 100 serotyped strains, uses intercellular adhesion molecule-1 (ICAM-1), whereas the “minor group” (~10% of the 100 serotyped strains) gains cell entry via the low-density lipoprotein receptor (LDLR)^{3,4}. RV-C (~60 non-serotyped strains) uses cadherin-related family 3 (CDHR3) for binding and replication⁵. The high number and variability of RV serotypes make vaccine design extremely challenging.

Nasal and bronchial epithelial cells are the first targets of RVs and are responsible for initiating anti-viral responses⁶. Viral recognition occurs via various pattern recognition receptors (PRRs), including RIG-I-like receptors (RLRs) and Toll-like receptors (TLRs), which induce the production of inflammatory mediators and interferons (IFNs). The role of IFNs is important for the control of RV infection, as they induce anti-viral IFN-stimulated genes and inflammatory mediators which limit viral replication (the role of inflammatory mediators during RV infection and asthma has recently been reviewed^{6,7}). This inflammatory “cascade” induces the recruitment and activation of innate cells which can affect the phenotype of adaptive responses. RVs enhance interleukin-25 (IL-25), IL-33, and thymic stromal lymphopoietin (TSLP) which drive type 2 immune responses^{8–11}. Increasing evidence suggests that the recognition of RVs, the type of innate cells, and the production of inflammatory mediators can drive the phenotype of immune responses. This commentary focuses on very recent advances made in understanding how innate/adaptive immune responses drive RV-induced asthma exacerbations.

Rhinovirus infection

RVs are positive-sense, single-stranded RNA (ssRNA) viruses belonging to the *Picornaviridae* family and *Enterovirus* genus. RVs are the most common cause of upper respiratory tract infection and are linked to exacerbations of COPD and asthma. Furthermore, they are the cause of bronchiolitis in infants and lower respiratory tract infections in children, the immunosuppressed, and the elderly⁴. About 160 serotypes/strains of RV have been identified and are classified into three species: RV-A (74 serotypes), RV-B (25 serotypes), and RV-C (~60 strains)^{12–14}. RV-C species were the last to be identified and are responsible for more severe illness, wheezing, and asthma exacerbations^{3,4}. The RV viral capsid sequence variation causes the antigenic diversity between strains. The viral capsid is composed of VP1, VP2, VP3, and VP4 proteins. VP1 and VP3 are important for viral attachment to cell surface receptors in ciliated nasal and bronchial epithelial cells^{15,16}.

Large-scale birth cohort studies identify a relationship between wheezing RV infections in early life and development

of asthma later in high-risk children¹⁷. RV-C infections are associated with severe infection in children, and a *CDHR3* gene mutation can mediate enhanced RV-C entry to host cells⁵. Recent clinical evidence, from two birth cohorts, suggests that a *CDHR3* mutation is an asthma risk allele associated with enhanced RV-C illness¹⁸. Targeting the interaction between RV and respective adhesion receptors can provide a therapeutic avenue. The precise mechanisms by which RVs induce asthma exacerbation are unclear. Impaired anti-viral immunity can influence the onset of infection in bronchial epithelial cells (BECs) derived from patients with asthma^{19–21}. Furthermore, evidence suggests that multiple immunophenotypes of immune responses to RV exist in childhood that enhance asthma development²². Improved understanding of how RV infection drives the phenotype of infection can help distinguish potential therapeutic and vaccine targets against RV-induced asthma exacerbations.

Innate recognition of rhinovirus

Following RV infection of airway epithelial cells, a series of cellular PRRs can recognise viral antigens. TLR2 on the cell surface recognises viral capsid proteins²³. Within the endosome, TLR3 and TLR7/8 recognise viral double-stranded RNA (dsRNA) or ssRNA, respectively^{24,25}. The recognition of RV by TLR3 in BECs also induces the expression of RIG-I and MDA5, which can recognise ssRNA and dsRNA, respectively²³. Recognition of RV by PRRs causes the secretion of inflammatory cytokines, including IL-6, tumour necrosis factor, IL-12, IL-15, and type I and type III IFNs. This also drives the secretion of chemokines such as CXCL10 (IP-10) and CXCL8/IL-8 which drive the recruitment of T cells—monocytes, natural killer cells, and dendritic cells (DCs) are also recruited—and neutrophils, respectively²⁶. Further to IFNs and inflammatory cytokines, epithelial cells are also a source of IL-33, IL-25, and TSLP, all of which can drive T helper type 2 (Th2) cell responses during RV infection (RV-induced cytokines have been extensively reviewed^{6,7,27}). Evidence suggests that anti-viral defence within bronchial epithelium requires co-ordinated recognition of RV²⁸.

The events that occur during innate recognition may help understand how asthma and COPD exacerbations develop after RV infection. Primary BECs from patients with asthma have a deficiency in TLR3 and MDA5 signalling, which reduces the production of inflammatory mediators after RV infection^{25,26}. TLR3 expression in asthma is not impaired, and blocking the receptor in mice does not have a significant effect in reducing viral replication^{26,29}. In contrast, blockade of TLR3, using CNT03157, in healthy volunteers reduces the production of inflammatory mediators and cellular recruitment after RV16 infection (thus reducing cold symptoms); however, it had no effect in asthma³⁰.

TLR7/8 are expressed in a number of lung cells, including epithelial cells, macrophages, and DC subsets. Plasmacytoid DCs (pDCs) respond rapidly to TLR7 ligation and induce type I IFN production because of a constitutive expression of IFN regulatory factor-7 (IRF-7)^{31,32}. The mechanisms behind why the production of IFNs in asthma is impaired during RV infection are poorly understood. RV infection of mice with impaired TLR7

signalling showed a reduced production of IFNs, eosinophilia, and airway hyper-reactivity²⁴. The effects were reversed by adoptive transfer of TLR7-competent pDCs or exogenous IFN. Furthermore, Th2 cytokine induction after RV infection is a negative regulator of TLR7- or TLR3-induced IFNs²⁴. The induction of IL-4 and IL-13 inhibits the expression of TLR3 and IRF-3 and impairs the immune responses of epithelial cells against RVs³³. These observations support evidence that patients with severe asthma have reduced TLR7 expression and IFN production in the bronchoalveolar lavage^{34,35}. Overall, complex innate recognition is involved during RV infection with a co-ordinated recognition, and an early robust IFN response and balance in the inflammatory mediators are essential for viral clearing and minimising RV-induced morbidity^{21,33}.

Interplay between innate and adaptive responses drives rhinovirus-induced exacerbations

Recognition of RV antigens by T cells initiates cytotoxic T-cell responses and activates T helper cells that drive humoral responses. Upon infection, epithelial cells, macrophages, and recruited neutrophils secrete CXCL10 (IP-10), which increases the chemotaxis of T cells^{4,36}. The type of T-cell response toward RV is one of the factors driving asthma exacerbations³⁷. In healthy individuals, the primary immune responses to RV infection are T helper type 1 (Th1) and are characterised by a release of IFN- γ ³⁸. Th2 immune responses are characterised by increased production of IL-4, IL-5, and IL-13 and have been associated with RV infection in asthma^{6,10,37,38}. Cytokines inducing Th2 responses provide a potential therapeutic target. For example, dupilumab (IL-4 and IL-13 signalling inhibitor) significantly reduces the rates of severe asthma exacerbations and improves lung function in patients³⁹. Recent studies also indicate an increasingly important role for innate lymphoid cells (ILCs) in driving RV infections^{10,40–42}. Specifically, ILC2s are elevated in patients with asthma and are potent producers of type 2 cytokines, which can drive adaptive immune responses^{6,27,42,43}.

Immune responses to respiratory infections in healthy individuals are typically characterised by a Th1 immune response. However, RV-driven asthma exacerbations are additionally characterised by an amplified Th2 immune response and airway neutrophilia⁴⁴. Neutrophil degranulation and elastase release in the airways are believed to contribute to obstruction in the lower airways in RV-induced asthma exacerbations⁴⁵. The mechanisms behind how RV drives Th2 immune responses during asthma exacerbations were recently studied^{8,10,11,46}. RVs can induce a number of inflammatory mediators that drive Th2 responses in asthma exacerbations. IL-25 is an important mediator in RV-induced asthma exacerbations^{47,48}. Primary BECs from patients with asthma have increased expression of IL-25, which correlates with the donor atopic status. In mice, blocking the IL-25R following RV infection reduces mucus secretion, airway hyper-responsiveness, and secretion of Th2 cytokines⁸. The role for IL-33 in driving RV-induced asthma exacerbations was examined in a human experimental model of RV¹⁰. RV infection correlated with the inductions of Th2 cytokines and IL-33. Furthermore, infection of primary BECs with RV induced IL-33 secretion. Supernatant transfer from the

infected BECs to human T cells or ILC2s strongly induced Th2 responses¹⁰. The importance of IL-33 in driving Th2 immune responses is supported by mouse models with deficiencies in the IL-33 pathways⁹. Human lung epithelial cells infected with RV secrete IL-33 and TSLP¹¹. Furthermore, mice that are simultaneously exposed to ovalbumin and RV show a reduction in regulatory T-cell activation. This reduction is associated with increased Th2 responses and a prevention of ovalbumin tolerance that are driven by IL-33 and TSLP^{11,27}. In humans with uncontrolled asthma, the inhibition of Th2 responses using tezepelumab (monoclonal antibody specific for TSLP) reduces the rates of asthma exacerbations in patients with asthma inadequately treated with long-acting beta-agonists and medium to high doses of inhaled corticosteroids⁴⁹. Overall, these studies show the pivotal role of cytokines secreted by epithelial cells in driving the type of innate and adaptive immune responses during RV infection.

In the past few decades, neutrophils have been shown to form neutrophil extracellular traps (NETs) in order to trap invading pathogens such as bacteria through the release of dsDNA, antimicrobial proteins, and histones. The regulation of these NETs is driven by neutrophil elastase and myeloperoxidase^{50–52}. In addition to trapping bacterial pathogens, NETs have an increasingly important role during viral infections⁵³. The presence of NETs after RV infection and the role they have in driving Th2 immune responses were studied in mice and humans⁴⁶. RV infection induces NET-associated dsDNA in humans. Patients with asthma challenged with RV-16 showed higher levels of lavage dsDNA, which correlated with cold symptom severity, presence of Th2 cytokines, and asthma exacerbation. Using a mouse allergen-induced model, the same authors showed that RV-infected allergic mice have higher levels of lavage dsDNA in the airways^{46,54}. When these mice were treated with DNase (to remove NETs) or elastase inhibitors (to prevent NET formation), the Th2 immune responses, production of cytokines, and cell recruitment were diminished. Evidence suggests that NET formation can provide a novel therapeutic target by which DNase, elastase inhibitors, and neutrophil trafficking inhibitors can be used during RV-induced asthma exacerbations.

Multiple asthma mouse models improved understanding of the mechanisms involved in driving Th2 responses during RV infection. The role of $\gamma\delta$ T cells was studied in human and animal models⁵⁵. Levels of $\gamma\delta$ T cells are elevated in asthma and asthma mouse models. Blocking $\gamma\delta$ T cells in mice enhanced Th2 immune cell recruitment to the airways. Overall, the data suggest that $\gamma\delta$ T cells are negative regulators of disease during RV-induced asthma exacerbations⁵⁵. To further characterise the importance of T-cell responses, mice deficient in T-Box expressed in T cells (Tbet), a controller of Th1 cells, were studied in an RV infection model. Mice that lacked Tbet developed a Th2/Th17 phenotype after RV infection⁵⁶. The lack of Th1 responses is associated with increased viral load, eosinophilia, and mucus production. These findings suggest that weakened Th1 responses, with consequent Th2/Th17 responses, may have an important role in driving allergic features during RV asthma exacerbations⁵⁶. The phenotype of T helper cell responses is

critical for the outcome of RV infection. The recruitment of Th1 cells and the relevant production of IFN- γ have been linked to efficient viral clearance. Studies suggest that viral shedding is inversely related to T-cell counts in the airways⁴. Finally, an interesting feature of T-cell immunity against RV infections is that they can become activated by shared viral epitopes which can allow potent responses across serotypes⁵⁷.

Vaccine approaches against rhinovirus

For decades, vaccine development against RVs has been considered almost impossible⁵⁸. The large breadth of RV serotypes is a major obstacle in developing therapy. Neutralising humoral responses against RV infection are associated with protection; however, the mechanisms of their induction are poorly understood. Upon RV infection, IgG and IgA are observed in the serum and the airways, respectively⁵⁹. High levels of serotype-specific antibodies are associated with protection. Despite this, the main limiting factor with humoral responses against RV is that, owing to the high number of serotypes, little cross-reactivity is elicited by neutralising antibodies⁶⁰.

Recent advances in understanding RV serotypes and viral capsid structures provide promising vaccine targets. The amino acid identity within RV serotypes is at 70%, and VP1 and VP4/VP2 (VP0) capsid regions are the most conserved⁶¹. A recombinant

VP0 vaccine in conjunction with an IFA/CpG adjuvant in mice elicited strong cross-reactive Th1 responses and, following virus challenge, enhanced neutralising antibody responses within the serotype⁶². The usage of immunogens, such as VP0, in combination with Th1-promoting adjuvants provides a promising avenue for RV vaccine development^{60,63}. The main limitation with vaccines against RV is increasing the breadth of the immune responses across other serotypes. For example, vaccination of rabbits with VP1/VP3 increases neutralising antibodies only within a specific group of serotypes⁶⁴. Taken together, these results highlight the difficulty for a single antigen providing protection across all RV serotypes⁶⁵. Through the use of an adjuvanted polyvalent RV vaccine in macaques and mice, the induction of neutralising antibodies across a diverse range of RV serotypes is feasible⁶⁴. The identification of conserved regions within the RV genome and production of an adjuvanted polyvalent RV vaccine provide exciting pathways for RV vaccine development. Overall, recent advances in understanding RV immunity increase hopes that a vaccine may be feasible after all.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References



- Johnston SL, Pattermore PK, Sanderson G, *et al.*: **Community study of role of viral infections in exacerbations of asthma in 9-11 year old children.** *BMJ*. 1995; **310**(6989): 1225–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ferreira A, Williams Z, Donninger H, *et al.*: **Rhinovirus is associated with severe asthma exacerbations and raised nasal interleukin-12.** *Respiration*. 2002; **69**(2): 136–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Palmenberg AC, Gern JE: **Classification and evolution of human rhinoviruses.** *Methods Mol Biol*. 2015; **1221**: 1–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Jacobs SE, Lamson DM, St George K, *et al.*: **Human rhinoviruses.** *Clin Microbiol Rev*. 2013; **26**(1): 135–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bochkov YA, Watters K, Ashraf S, *et al.*: **Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication.** *Proc Natl Acad Sci U S A*. 2015; **112**(17): 5485–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Edwards MR, Strong K, Cameron A, *et al.*: **Viral infections in allergy and immunology: How allergic inflammation influences viral infections and illness.** *J Allergy Clin Immunol*. 2017; **140**(4): 909–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rowe RK, Gill MA: **Effects of Allergic Sensitization on Antiviral Immunity: Allergen, Virus, and Host Cell Mechanisms.** *Curr Allergy Asthma Rep*. 2017; **17**(2): 9.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
- Beale J, Jayaraman A, Jackson DJ, *et al.*: **Rhinovirus-induced IL-25 in asthma exacerbation drives type 2 immunity and allergic pulmonary inflammation.** *Sci Transl Med*. 2014; **6**(256): 256ra134.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Barlow JL, Peel S, Fox J, *et al.*: **IL-33 is more potent than IL-25 in provoking IL-13-producing nuocytes (type 2 innate lymphoid cells) and airway contraction.** *J Allergy Clin Immunol*. 2013; **132**(4): 933–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Jackson DJ, Makrinioti H, Rana BM, *et al.*: **IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo.** *Am J Respir Crit Care Med*. 2014; **190**(12): 1373–82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Mehta AK, Duan W, Doerner AM, *et al.*: **Rhinovirus infection interferes with induction of tolerance to aeroantigens through OX40 ligand, thymic stromal lymphopoietin, and IL-33.** *J Allergy Clin Immunol*. 2016; **137**(1): 278–288.e6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Lamson D, Renwick N, Kapoor V, *et al.*: **MassTag polymerase-chain-reaction detection of respiratory pathogens, including a new rhinovirus genotype, that caused influenza-like illness in New York State during 2004-2005.** *J Infect Dis*. 2006; **194**(10): 1398–402.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Palmenberg AC, Spiro D, Kuzmickas R, *et al.*: **Sequencing and analyses of all known human rhinovirus genomes reveal structure and evolution.** *Science*. 2009; **324**(5923): 55–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Bochkov YA, Gern JE: **Clinical and molecular features of human rhinovirus C.** *Microbes Infect*. 2012; **14**(6): 485–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Yamaya M, Nomura K, Arakawa K, *et al.*: **Increased rhinovirus replication in nasal mucosa cells in allergic subjects is associated with increased ICAM-1 levels and endosomal acidification and is inhibited by L-carbocysteine.** *Immun Inflamm Dis*. 2016; **4**(2): 166–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Blaas D, Fuchs R: **Mechanism of human rhinovirus infections.** *Mol Cell Pediatr*. 2016; **3**(1): 21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Jackson DJ, Gangnon RE, Evans MD, *et al.*: **Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children.** *Am J Respir Crit Care Med*. 2008; **178**(7): 667–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Bønnelykke K, Coleman AT, Evans MD, *et al.*: **Cadherin-related Family Member 3 Genetics and Rhinovirus C Respiratory Illnesses.** *Am J Respir Crit Care Med*. 2018; **197**(5): 589–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Contoli M, Message SD, Laza-Stanca V, *et al.*: **Role of deficient type III**

- interferon-lambda production in asthma exacerbations. *Nat Med*. 2006; 12(9): 1023–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
20. Edwards MR, Regamey N, Vareille M, *et al.*: Impaired innate interferon induction in severe therapy resistant atopic asthmatic children. *Mucosal Immunol*. 2013; 6(4): 797–806.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 21. Wark PA, Johnston SL, Bucchieri F, *et al.*: Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med*. 2005; 201(6): 937–47.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 22. Custovic A, Belgrave D, Lin L, *et al.*: Cytokine Responses to Rhinovirus and Development of Asthma, Allergic Sensitization, and Respiratory Infections during Childhood. *Am J Respir Crit Care Med*. 2018; 197(10): 1265–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 23. Triantafyllou K, Vakakis E, Richer EA, *et al.*: Human rhinovirus recognition in non-immune cells is mediated by Toll-like receptors and MDA-5, which trigger a synergetic pro-inflammatory immune response. *Virulence*. 2011; 2(1): 22–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 24. Hatchwell L, Collison A, Girkin J, *et al.*: Toll-like receptor 7 governs interferon and inflammatory responses to rhinovirus and is suppressed by IL-5-induced lung eosinophilia. *Thorax*. 2015; 70(9): 854–61.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 25. Parsons KS, Hsu AC, Wark PA: TLR3 and MDA5 signalling, although not expression, is impaired in asthmatic epithelial cells in response to rhinovirus infection. *Clin Exp Allergy*. 2014; 44(1): 91–101.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. Wang Q, Miller DJ, Bowman ER, *et al.*: MDA5 and TLR3 initiate pro-inflammatory signaling pathways leading to rhinovirus-induced airways inflammation and hyperresponsiveness. *PLoS Pathog*. 2011; 7(5): e1002070.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 27. Farne HA, Johnston SL: Immune mechanisms of respiratory viral infections in asthma. *Curr Opin Immunol*. 2017; 48: 31–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 28. Slater L, Bartlett NW, Haas JJ, *et al.*: Co-ordinated role of TLR3, RIG-I and MDA5 in the innate response to rhinovirus in bronchial epithelium. *PLoS Pathog*. 2010; 6(11): e1001178.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 29. Sykes A, Edwards MR, Macintyre J, *et al.*: Rhinovirus 16-induced IFN- α and IFN- β are deficient in bronchoalveolar lavage cells in asthmatic patients. *J Allergy Clin Immunol*. 2012; 129(6): 1506–1514.e6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. Silkoff PE, Flavin S, Gordon R, *et al.*: Toll-like receptor 3 blockade in rhinovirus-induced experimental asthma exacerbations: A randomized controlled study. *J Allergy Clin Immunol*. 2018; 141(4): 1220–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. **F** Xi Y, Troy NM, Anderson D, *et al.*: Critical Role of Plasmacytoid Dendritic Cells in Regulating Gene Expression and Innate Immune Responses to Human Rhinovirus-16. *Front Immunol*. 2017; 8: 1351.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 32. Honda K, Yanai H, Negishi H, *et al.*: IRF-7 is the master regulator of type-I interferon-dependent immune responses. *Nature*. 2005; 434(7032): 772–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 33. **F** Contoli M, Ito K, Padovani A, *et al.*: Th2 cytokines impair innate immune responses to rhinovirus in respiratory epithelial cells. *Allergy*. 2015; 70(8): 910–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 34. **F** Rupani H, Martinez-Nunez RT, Dennison P, *et al.*: Toll-like Receptor 7 Is Reduced in Severe Asthma and Linked to an Altered MicroRNA Profile. *Am J Respir Crit Care Med*. 2016; 194(1): 26–37.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 35. Shikhagaie MM, Andersson CK, Mori M, *et al.*: Mapping of TLR5 and TLR7 in central and distal human airways and identification of reduced TLR expression in severe asthma. *Clin Exp Allergy*. 2014; 44(2): 184–96.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Wark PA, Bucchieri F, Johnston SL, *et al.*: IFN-gamma-induced protein 10 is a novel biomarker of rhinovirus-induced asthma exacerbations. *J Allergy Clin Immunol*. 2007; 120(3): 586–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. **F** Message SD, Laza-Stanca V, Mallia P, *et al.*: Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production. *Proc Natl Acad Sci U S A*. 2008; 105(36): 13562–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 38. Steinke JW, Liu L, Turner RB, *et al.*: Immune surveillance by rhinovirus-specific circulating CD4⁺ and CD8⁺ T lymphocytes. *PLoS One*. 2015; 10(1): e0115271.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 39. **F** Castro M, Corren J, Pavord ID, *et al.*: Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med*. 2018; 378(26): 2486–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 40. **F** Głobińska A, Kowalski ML: Innate lymphoid cells: The role in respiratory infections and lung tissue damage. *Expert Rev Clin Immunol*. 2017; 13(10): 991–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 41. **F** Hong JY, Bentley JK, Chung Y, *et al.*: Neonatal rhinovirus induces mucous metaplasia and airways hyperresponsiveness through IL-25 and type 2 innate lymphoid cells. *J Allergy Clin Immunol*. 2014; 134(2): 429–39.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 42. **F** Dhariwal J, Cameron A, Trujillo-Torralbo MB, *et al.*: Mucosal Type 2 Innate Lymphoid Cells Are a Key Component of the Allergic Response to Aeroallergens. *Am J Respir Crit Care Med*. 2017; 195(12): 1586–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 43. **F** Withers DR: Innate lymphoid cell regulation of adaptive immunity. *Immunology*. 2016; 149(2): 123–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 44. Ritchie AI, Farne HA, Singanayagam A, *et al.*: Pathogenesis of Viral Infection in Exacerbations of Airway Disease. *Ann Am Thorac Soc*. 2015; 12 Suppl 2: S115–32.
[PubMed Abstract](#)
 45. Wark PA, Johnston SL, Moric I, *et al.*: Neutrophil degranulation and cell lysis is associated with clinical severity in virus-induced asthma. *Eur Respir J*. 2002; 19(1): 68–75.
[PubMed Abstract](#) | [Publisher Full Text](#)
 46. Toussaint M, Jackson DJ, Swieboda D, *et al.*: Host DNA released by NETosis promotes rhinovirus-induced type-2 allergic asthma exacerbation. *Nat Med*. 2017; 23(6): 681–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 47. Corrigan CJ, Wang W, Meng Q, *et al.*: Allergen-induced expression of IL-25 and IL-25 receptor in atopic asthmatic airways and late-phase cutaneous responses. *J Allergy Clin Immunol*. 2011; 128(1): 116–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
 48. Ballantyne SJ, Barlow JL, Jolin HE, *et al.*: Blocking IL-25 prevents airway hyperresponsiveness in allergic asthma. *J Allergy Clin Immunol*. 2007; 120(6): 1324–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. **F** Corren J, Parnes JR, Wang L, *et al.*: Tezepelumab in Adults with Uncontrolled Asthma. *N Engl J Med*. 2017; 377(10): 936–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 50. **F** Brinkmann V, Reichard U, Goosmann C, *et al.*: Neutrophil extracellular traps kill bacteria. *Science*. 2004; 303(5663): 1532–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 51. Papayannopoulos V, Metzler KD, Hakkim A, *et al.*: Neutrophil elastase and myeloperoxidase regulate the formation of neutrophil extracellular traps. *J Cell Biol*. 2010; 191(3): 677–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 52. **F** Papayannopoulos V: Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol*. 2018; 18(2): 134–47.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 53. **F** Schönrich G, Raftery MJ: Neutrophil Extracellular Traps Go Viral. *Front Immunol*. 2016; 7: 366.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 54. **F** Bartlett NW, Walton RP, Edwards MR, *et al.*: Mouse models of rhinovirus-induced disease and exacerbation of allergic airway inflammation. *Nat Med*. 2008; 14(2): 199–204.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 55. Glanville N, Message SD, Walton RP, *et al.*: $\gamma\delta$ T cells suppress inflammation and disease during rhinovirus-induced asthma exacerbations. *Mucosal Immunol*. 2013; 6(6): 1091–100.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 56. Glanville N, Peel TJ, Schröder A, *et al.*: Tbet Deficiency Causes T Helper Cell Dependent Airways Eosinophilia and Mucus Hypersecretion in Response to Rhinovirus Infection. *PLoS Pathog*. 2016; 12(9): e1005913.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 57. Gern JE, Dick EC, Kelly EA, *et al.*: Rhinovirus-specific T cells recognize both shared and serotype-restricted viral epitopes. *J Infect Dis*. 1997; 175(5): 1108–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
 58. Papi A, Contoli M: Rhinovirus vaccination: the case against. *Eur Respir J*. 2011; 37(1): 5–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 59. Barclay WS, al-Nakib W, Higgins PG, *et al.*: The time course of the humoral immune response to rhinovirus infection. *Epidemiol Infect*. 1989; 103(3): 659–69.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 60. Glanville N, Johnston SL: Challenges in developing a cross-serotype rhinovirus vaccine. *Curr Opin Virol*. 2015; 11: 83–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 61. **F** Stobart CC, Nosek JM, Moore ML: Rhinovirus Biology, Antigenic Diversity, and Advancements in the Design of a Human Rhinovirus Vaccine. *Front Microbiol*. 2017; 8: 2412.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

62. Glanville N, McLean GR, Guy B, *et al.*: **Cross-serotype immunity induced by immunization with a conserved rhinovirus capsid protein.** *PLoS Pathog.* 2013; **9**(9): e1003669.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
63. Williams GR, Kubajewska I, Glanville N, *et al.*: **The potential for a protective vaccine for rhinovirus infections.** *Expert Rev Vaccines.* 2016; **15**(5): 569–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
64.  Lee S, Nguyen MT, Currier MG, *et al.*: **A polyvalent inactivated rhinovirus vaccine is broadly immunogenic in rhesus macaques.** *Nat Commun.* 2016; **7**: 12838.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
65. Schlingmann B, Castiglia KR, Stobart CC, *et al.*: **Polyvalent vaccines: High-maintenance heroes.** *PLoS Pathog.* 2018; **14**(4): e1006904.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:



Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the reviewers provide input before publication and only the final, revised version is published. The reviewers who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The reviewers who approved this article are:

Version 1

1 **Larry J Anderson**

Department of Pediatrics, Emory University, Atlanta, Georgia, USA

Competing Interests: No competing interests were disclosed.

2 **Ville Peltola**

Department of Pediatrics, University of Turku and University Hospital, Turku, Finland

Competing Interests: No competing interests were disclosed.

3 **Reena Ghidyal**

Centre for Research in Therapeutic Solutions, Faculty of Science and Technology, University of Canberra, Canberra, Australia

Competing Interests: No competing interests were disclosed.

4 **Zhao-Jun Duan**

National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, 102206, China

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research